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10/522,258	10/20/2005	Jens Lichtenberg	2815-0293PUS1	1480

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EXAMINER	
SZNAIDMAN, MARCOS L	
ART UNIT	**PAPER NUMBER**
1609	

NOTIFICATION DATE	DELIVERY MODE
10/03/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/522,258	LICHTENBERG ET AL.	
	Examiner	Art Unit	
	Marcos L. Sznaidman	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-22* is/are pending in the application.

4a) Of the above claim(s) *14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,13 and 15-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1 page*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of N-3,5-di(trifluoromethyl)phenyl-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl]urea in the reply filed on August 24, 2007 is acknowledged. The traversal is on the ground(s) that the members covered by the present claims are sufficiently few in number and so closely related that a search and examination of the claims can be made without serious burden. This is not found persuasive because: first: the number of compounds included in the general formula I of instant claim 12, when considered all possible permutations for groups R3, R4, R5, R6, R12, R13, R14, R15 and R16, could easily reach a billion compounds (even with the conservative estimate that each R group mentioned before, could have only 10 possible different substituents. In reality this number is much bigger, since each R group could represent at least a 100 different substituents based on the definitions of instant claim 12). Second: some of the substituents are defined with very broad and generic terms like: heteroaryl or phenyl substituted rings, where substituents are also broad and generic like 5 to 7-membered heterocyclic rings. Due to the diverse nature of the substituents, many of these compounds will encompass structures that are classified differently. Search of some of these compounds will not encompass the search for another structurally distinct compound represented by the general formula I of claim 12.

The requirement is still deemed proper and is therefore made FINAL.

Status of claims

Claims 12-22 are currently pending and are the subject of this office action. Claims 12-13 and 15-22 are currently under examination.

Claim 14 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on August 24, 2007.

Priority

The present application claims priority to international application No. PCT/DK03/00518 filed 07/31/2003, and to foreign applications DENMARK PA 2003 00371 filed 03/11/2003, DENMARK PA 2002 01839 filed 11/28/2002 and DENMARK PA 2002 01165 filed 08/01/2002. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-13 and 15-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one

skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1- the quantity of experimentation necessary,

2- the amount of direction or guidance provided,

3- the presence or absence of working examples,

4- the nature of the invention,

5- the state of the prior art,

6- the relative skill of those in the art,

7- the predictability of the art, and

8- the breadth of the claims

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

Claim 12 and its dependent claims (13, 15-17 and 21) recite "a method of treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including human, which disorder, disease or condition is responsive to inhibition of angiogenesis, comprising the step of administering...". Claims 18 and its dependent claims (19-20 and 22) recite "a method of treatment, prevention or alleviation of age-related macular degeneration of a living animal body, including a human comprising the step of administering to such living animal body, including human, in need thereof a therapeutically effective amount of a VRAC blocker or a pharmaceutically acceptable salt thereof".

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

The factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies with the degree of unpredictability of the factors involved", and prevention or alleviation of a disease or condition that is responsive to inhibition of angiogenesis, or prevention or alleviation of age-related macular degeneration, are considered to be unpredictable factors. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved), *Ex parte Sudilovsky* 21

USPQ2d 1702 (Applicant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable). Although prior art offers evidence for the treatment of angiogenesis related diseases like age-related macular degeneration, there is no evidence that any angiogenesis related disease could be prevented or alleviated by any treatment. As illustrative of the state of the art, the examiner cites Talmadge et. al. (The American Journal of Pathology (2007), 170, 793-804). It is clearly stated that there is low predictability between animal models and the development of drugs for the treatment of cancer, much less for the prevention or alleviation of this diseases.

2. The breadth of the claims

The claims vary in breadth; some (such as claim 12) vary broadly, reciting the treatment, prevention or alleviation of a disease or condition responsive to inhibition of angiogenesis, which covers a very broad genus of associated diseases (see claim 16 for a list of diseases claimed to be prevented or alleviated). It also claims to treat those diseases with a broad genus of compounds encompassed by structure I (claim12).

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification fails to disclose any data to support the fact that using this method could prevent or alleviate any disease responsive to angiogenesis. Applicant provides results for an *in vivo* anti-angiogenesis assay for two compounds. This assay

could be used as evidence for the possible use of this compounds in treating some angiogenesis related diseases, but not as a predictor of preventing or alleviating these diseases.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed genus of compounds could be predictably used for the prevention or alleviation of angiogenesis related diseases.

Only two compounds (**a** and **b**, see specification page 20, under examples) of the large genus claimed (see general structure I in claim 12) were tested *in vitro* and *in vivo* models. With such a broad genus, determining if any particular claimed compound would prevent or alleviate an angiogenesis related disease, would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it to clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by applicants.

Accordingly, the inventions of claims 12-13 and 15-22 do not comply with the enablement requirement of 35 U.S.C 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation with no assurance of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12-13 and 15-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Manolopoulos (General Pharmacology 34 (2000) 107-116, cited by the applicant) in view of Dahl et. al. (WO 00/24707, cited by the applicant).

Claims 12-13,15-17 and 21 recite "a method of treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to inhibition of angiogenesis, comprising the step of administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of a compound of general formula I (specifically: N-3,5-di(trifluoromethyl)phenyl-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl]urea)."

Claims 18-20 and 22 recite "a method of treatment, prevention or alleviation of age-related macular degeneration of a living animal body, including a human, comprising the step of administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of a VRAC blocker or a pharmaceutically acceptable salt thereof (specifically: N-3,5-di(trifluoromethyl)phenyl-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl]urea)."

Manolopoulos teaches that "VRAC blockers are potent inhibitors of angiogenesis and thus might serve as therapeutic tools in tumor growth and other angiogenesis dependent diseases (see abstract). Manolopoulos does not teach the specific use of N-3,5-di(trifluoromethyl)phenyl-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl]urea for the treatment of angiogenesis dependent diseases. However, Dahl et. al. teach that

compounds of general structure I (see abstract) and in particular of N-3,5-di(trifluoromethyl)phenyl-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl]urea (see page 36, 4th compound from the top) are useful as chloride channel blockers (Volume-Regulated Anion Channels (VRAC) are a subclass of chloride channels).

Since Manolopoulos teaches that VRAC blockers are useful for treating angiogenesis dependent diseases, and since Dahl et. al. teach that N-3,5-di(trifluoromethyl)phenyl-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl]urea is a VRAC blocker; at the time of the invention it would have been *prima facie* obvious for a person of ordinary skill in the art to select any VRAC inhibitor (in this case N-3,5-di(trifluoromethyl)phenyl-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl]urea) for treating any angiogenesis dependent disease (including those recited in claim 16 or age-related macular degeneration recited in claim 18. See Manopolopouls, first paragraph of the introduction where he recites many pathological processes associated with angiogenesis: diabetic retinopathy, arthritis, inflammation and the growth of several types of solid tumors), thus resulting in the practice of claims 12-13 and 15-22 with a reasonable expectation of success.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 12-13 and 15-22 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 21-22, 35, and 38-39 of copending Application No. 10/526,208. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications claim identical set of compounds (elected species N-3,5-di(trifluoromethyl)phenyl-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl]urea is a species of the Markush formulas I of claim 21 and of formula II of claim 22 of application No. 10/526,208), for identical methods of use: for example: disease or condition is responsive to the blockade of chloride ion channels (in claim 35 of application No. 10/526,208), and disorder or condition responsive to inhibition of angiogenesis (in claim 38 of application No. 10/526,208) or the method wherein the disease, disorder or condition responsive to the blockade of chloride channels is.... (see list of diseases in claim 39 of application No. 10/526,208).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed. Claims 12-13 and 15-22 are rejected under 35 U.S.C. 112 (first paragraph) and under 35 U.S.C. 103(a). Claims 12-13 and 15-22 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcos L. Sznaidman whose telephone number is 571 270-3498. The examiner can normally be reached on Monday through Friday 9 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on 571 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ardin H. Marschel 9/27/07

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER

MLS
September 17, 2007